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EXAMINER

WALICKA, MALGORZATA A

ART UNIT PAPER NUMBER

1652

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/423,554

Applicant(s)

ARISTIDOU ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25, 26 and 42-65 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25 and 26 is/are allowed.
- 6) ☒ Claim(s) 42-65 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 November 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11/05/03 . 6) ☐ Other: *See Continuation Sheet.*

Continuation of Attachment(s) 6). Other: copy of the patent used in 102 rejections.

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The Reply under 37 CFR § 1.111 and 1.114, filed on Nov. 5, is acknowledged. Amendments to the claims have been entered as requested. Claims 1-24 and 27-41 have been canceled. New claims 42-65 have been added. Claims 25, 26, and 42-65 are pending and are the subject of this Office Action.

Detailed Office Action

Declaration under 37 CFR section 1.132

Declaration under 37 CFR section 1.132 of Dr. John Londesborough is acknowledged. The newly filed claims have sufficient support in description of the enzymes provided in the declaration.

1. Objections

1.1. Specification

The disclosure is still objected. Although Applicants deleted the embedded hyperlink on see page 47, line 7 and 29, the amendment filed Nov.5, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the handbook quoted by Applicants was published after the priority and filing date of the application.

Applicant is required to cancel the new matter in the reply to this Office Action, or quote the earlier edition of the handbook.

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1.2. Claims

In claims 42, 43, the examiner suggests the phrase: "improving yield of a product from a production process" be replaced by "increasing yield of production of a product."

In claim 57, 62, 64, the examiner suggests the use of "increasing the yield" instead "improving the yield."

In claim 57, 60, 61, the examiner suggests replacement of the term "industrial product" by "product".

Claim 52 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The claim is directed to a method of production of a product from a group of quoted compounds, whereas the base claim 51 is not directed to such a method. The proper language for such a claim would be "The method of claim 51 further comprising producing a product etc."

The examiner proposes to use the term enzyme, instead of the term "protein" through the claims. If a protein has an enzymatic activity, as recited by claims (oxidizes, reduces), it is called in the art an enzyme.

2.1. 35 USC 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Rejection of claims 1-10, 17- 22, 28-30, 33, 38 and 39-41 under 35 U.S.C. 112, made or maintained in the previous Office Action is moot because the claims have been cancelled.

New claims 42-50 and 53-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42, 43 and 64 recite the limitation "microorganism" in the 6th line. There is insufficient antecedent basis for this limitation in the claims.

Claim 62 and 43, recite the limitation "microorganism" in the 3th line. There is insufficient antecedent basis for this limitation in the claims.

Claim 50, recites the limitation "microorganism" in the 4th line. There is insufficient antecedent basis for this limitation in the claim.

Claim 50 is unclear in recitation "a biotechnological process", which is not defined in the claim or in the specification.

Claim 57, recites the limitation "microorganism" in the 74th line. There is insufficient antecedent basis for this limitation in the claim.

Claim 42, 43, 44, 45, 46, 47, 48, 49, 50, 56, 62, 63 are confusing because of the use of the phrase "one or more of NADH and NADPH." There exist one NADH and one NADPH. Does the meaning of the claim is: "either or both of NADH and NADPH" or one or more molecules of NADH and NADPH" or something else?

Furthermore, the phrase "wherein said product is produced in a cell wherein the production process normally results in etc." in claim 42 and 64 is confusing, because the product is not produced in that cell; the product is produced in the transformant of that cell.

In addition, the phrase "polynucleotides that express a protein" in claim 42, 53-55, 62 is confusing. Polynucleotides encode proteins. Polynucleotides are expressed. For examination purposes it is assumed that the Applicants intended to recite polynucleotides that encode an enzyme."

Claim 54, 55 is rejected as reciting a phrase "a cellular process that normally results in depletion". It is unclear which process normally results in depletion and is to be prevented. In a living cell the processes do not result in depletion "etc.", because the cell would die. The meaning of the term normally is unclear rendering the claim unclear.

Claim 58 is confusing in recitation of the phrase "wherein the enzymes are dehydrogenases." Claim 57, from which claim 58 depends, explicitly recites "enzyme 4, which is not a dehydrogenase", therefore it is confusing how enzyme 4 can be not a dehydrogenase and a dehydrogenase at the same time.

2.2. 35 USC 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 42, 43, 45, 46, 48 and 50-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 and 48 are directed to a large genus of methods using any microorganism transformed with at least one polynucleotide that encodes and/or causes the expression of an enzyme, wherein said enzyme oxidizes or reduces one or more molecules NAD and NADP. The claimed genus of methods uses microorganisms transformed with a polynucleotide from any natural source, as well as artificial. The disclosure does not provide sufficient written description of such polynucleotides (DNA molecules).

Applicants disclosed the *S. cerevisiae* and *S. pombe* transformants enumerated in claim 25 and 26, as well as transformants of *Coryneform* bacterium, (see page 55 of the specification, wherein said transformants are transformed with one or more polynucleotides encoding enzymes selected from the group consisting of glutamate dehydrogenase, malic enzyme, aldehyde dehydrogenase, malate dehydrogenase, glycerol-phosphate dehydrogenase, xylose-1-dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, orotate reductase, and ferredoxin reductase. However, the disclosure fails to teach however, said transformants being transformed with other polynucleotides that oxidizes either or both NAD and NADP. The genus of such polypeptides is a large and variable genus and polynucleotides encoding the indicated enzymes do not provide identifying characteristics of the other species of the genus. Thus, because Applicants do not sufficiently describe the genus of polynucleotides to be used in the claimed genus of the methods, one skilled in the art is not convinced that the inventors, at the time the application was filled, had possession of the claimed invention.

Claim 43, 45 and 46 are directed to a large genus of methods of production a product, using any microorganism transformed with at least one polynucleotide that encodes and/or causes the expression of an enzyme, wherein said enzyme oxidizes or reduces either or both NAD and NADP. The claims are directed to genus of methods of productions of a large genus of products for which lack a sufficient description in the specification. The disclosure teaches only the following products, i.e. species of the

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genus of product produced when the cofactors involved are NAD and NADPH: ethanol, xylitol, lysine, alanine, cysteine, aspartate, asparagines, glycine, isoleucine, leucine, methionine, praline, arginine, serine, threonine, valine tryptophan, and polyhydrobutyrate. This is, however not sufficient for identifying characteristics of other species of the genus of products.

Thus, because Applicants do not sufficiently describe the genus of products according to the claimed invention, one skilled in the art is not convinced that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 50- 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for maintaining either or both of ratio of a NADH/NAD cofactor pair at about 0.9 or of a NADPH/NADP cofactor pair at about 3.2 in a yeast cell during a biotechnological process or to a method of preventing depletion of NAD, NADH, NADP and NADPH in a cellular process. The claimed invention was has not been presented in the specification or in claims as originally filed. Thus, claims 50-55 introduce new matter. One skilled in the relevant is, therefore, not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 56 is rejected for lack of written description of the increase in at least one of NAD and NADPH cofactors recited by claim 42. The disclosure does not teach any measurements of the concentration of NAD and NADPH cofactors in any transformant used for production of product of claim 42. Claim 56 is directed to the method described in terms of general concept. This concept was not reduced to practice by measurement of the cofactor concentration in any of the production processes and transformants used. Therefore, the claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2.3. 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 42, 43, 44, 45, 46, 47, 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated by the US Patent 5,424,202 issued on June 13, 1995; copy enclosed.

Claims 62 and 63 are directed to the genus of methods of improving yield of product from a process wherein said product is produced in a microorganism transformed with one or more polynucleotides that encodes an enzyme, wherein said

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enzyme oxidizes one or more of NADH and NADPH or reduces one or more NADH and NADPH molecules thereby obtaining an increase in the yield of said product, compared to the yield of the process using the untransformed microorganism and wherein said transformants are transformed with one or more polynucleotides encoding enzymes selected from the group consisting of glutamate dehydrogenase, malic enzyme, aldehyde dehydrogenase, malate dehydrogenase, glycerol-phosphate dehydrogenase, xylose-1-dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, orotate reductase, and ferredoxin reductase and wherein said product is selected from the group of ethanol, xylitol, lysine, alanine, cysteine, aspartate, asparagines, glycine, isoleucine, leucine, methionine proline, arginine, serine, threonine, valine, tryptophan, and polyhydrobutyrate.

The patent discloses a species of the genus of methods disclosed by Applicants, because the patent discloses production of ethanol in a transformant of *Klebsiella pneumoniae* comprising the ethanol dehydrogenase gene adhB from *Z. mobilis* wherein the transformant produces ethanol more efficiently than the untransformed control (see Table 11 of the patent) using glucose or xylose as a carbohydrate source. Thus, the Patent describes a microorganism transformed with one of the polynucleotides encoding enzymes selected from the group consisting of glutamate dehydrogenase, malic enzyme, aldehyde dehydrogenase, malate dehydrogenase, glycerol-phosphate dehydrogenase, xylose-1-dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, orotate reductase, and ferredoxin reductase because the polynucleotide in the patent encodes alcohol dehydrogenase. The teaches

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production of one of the produce selected from the group of ethanol, xylitol, lysine, alanine, cysteine, aspartate, asparagines, glycine, isoleucine, leucine, methionine, proline, arginine, serine, threonine, valine, tryptophan, and polyhydrobutyrate, because **the patent teaches production of ethanol.**

Finally, the patent teaches the polynucleotide that encodes the enzyme wherein said enzyme oxidizes one or more of NADH and NADPH molecules or reduces one or more NADH and NADPH molecules, because alcohol dehydrogenase oxidizes 2 molecules NADH when producing 2 molecules of ethanol from two molecules of acetaldehyde, see the equation in column 7, line 13 of the patent.

With regards to claims 42, 43, 44, 45, 46, 47, 64 and 65 the patent discloses the invention wherein the ethanol is produced in a transformed microorganism wherein the production of ethanol in untransformed microorganism results in unbalanced production of at least one of NAD, NADH, NADP, NAPH or depletion of at least NAD and NAD PH cofactors (additional limitation of claim 64 - 65 and 42, 43, 44, 45, 46, 47).

The three enzymatic steps for production of ethanol from glucose are presented in column 6 and 7 of the patent.

The first step is this transformation of glucose into pyruvate is (column 6, line 42):



The second step is



The third step is



For continuation of glycolysis after step one the NAD^+ consumed by glycolysis must be regenerated by the oxidation of NADH, i.e. **step one is a production process that results in depletion or an unbalanced production of at least one of NAD, NADH, NADP, NAPH, because it results in depletion of NAD or unbalanced production of NADH. Alcohol dehydrogenase oxidases NADH to NAD^+** thus recovers depletion of NAD and unbalanced production of NADPH. That results in obtaining an increase in the yield of production ethanol compared to the yield of the process using untransformed microorganism; see results for no plasmid and with adhB containing plasmid in Table 11 of the Patent.

In summary, the patent teaches species of the genus of inventions disclosed by Applicants, thus the invention of the patent anticipates the genus of invention of the instant application; therefore, the claims are rejected.

3. Conclusion

Claims 25 and 26 are allowed or reasons stated in the previous Office Action, papers No. 10, 13, 15 and 19. Applicants are advised that claims directed to the use of transformants of claim 25 and 26 contain allowable subject matter; for example the method of production of ethanol by the yeast transformants of claim 25 and 26 is fully described and enabled. Production of xylitol by transformants of claim 25 and 36 and production of polyhydroxybutyrates by genetically engineered *S. cerevisiae* is also described, similarly production of lysine and other amino acids by transformed *Corynebacterium*; Example 23, Table 4 of the specification.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

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Patent Examiner



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